Prostate-specific Antigen Concentration: Influence of Age and Ethnicity

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This pilot study evaluated the influence of age and ethnicity on serum prostate-specific antigen (PSA) concentration in Asian and white men without a clinical diagnosis of prostate cancer. Between October and December 1993, 1260 patients who underwent serum PSA determination (Hybritech Tandem-R assay, San Diego, California) at Straub Clinic & Hospital were retrospectively analyzed. Of these, 885 (70%) men aged 40 to 79 years were either Asian (Chinese, Filipino, Japanese, and Korean) or white and had a serum PSA less than 10.0 ng/ml. The PSA for the entire group was 2.1 +/- 2.0 ng/ml (mean +/- SD). PSA correlated with age (r=0.31, p=0.0001) and age accounted for 10% of the variance in serum PSA. Using the regression formula, serum PSA increased 2.5% (0.06 ng/ml) per year of age. The entire study group was about equally divided between whites (49%) and Asians (51%). Nearly three-fourths of the Asian men were Japanese. The mean PSA was very close in the Asian and white groups. There was no direct correlation between serum PSA and ethnicity (r=0.03; p=0.3201). Ethnicity contributed 0.1% of the variance in PSA. In conclusion, this preliminary study suggests serum PSA increases with age in Asian and white men without a clinical diagnosis of prostate cancer. No difference was found in PSA between men of Asian and white ethnicity.

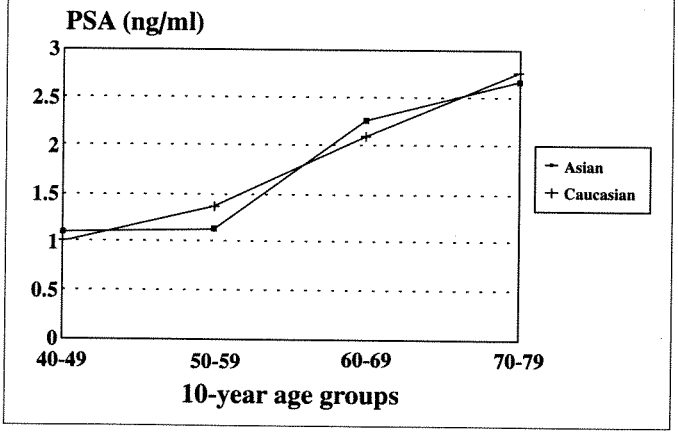
Introduction

Prostate carcinoma is an increasing medical problem in the United States. Prostate cancer is the most frequent nonskin cancer among men in the U.S., with 244,000 new cases and 40,400 deaths estimated for 1995.[1] In Hawaii, 790 new cases and 140 deaths are estimated for this year. Prostate-specific antigen is a protease secreted almost exclusively by the prostate epithelium. Blood levels are increased when normal glandular structure is disrupted by benign or malignant tumor, inflammation, or trauma due to cystoscopy or biopsy. The serum PSA level is directly proportional to tumor volume, with a greater increase per unit volume of cancer compared with benign prostatic hyperplasia.[2] However, PSA is not sufficiently sensitive or specific to be the ideal method of screening for prostate cancer. Approximately 25% of men with benign prostatic hyperplasia have an elevated serum PSA level.[3-4] Conversely, not all prostate cancers give rise to an elevated serum PSA concentration. Approximately 40% of men with organ-confined prostate cancer who undergo radical prostatectomy for potential cure have a normal serum PSA value using the conventional reference range.

The standard normal reference range for PSA (Hybritech Tandem-R assay, San Diego, California) is 0.0-4.0 ng/ml. Myrtle et al derived the upper limit of normal in a population of 472 apparently healthy, asymptomatic men.[5] No PSA values exceeded 10.0 ng/ml and 99% were less than 4.0 ng/ml. All men less than 40 years of age and 97% of men 40 years or older had a serum PSA less than or equal to 4.0 ng/ml. Recently Dalkin and co-workers conducted a study to refine the upper limits of PSA by age in men older than 50 years.[6] The new upper limits were 3.5 ng/ml for the 50-59 year old group, 5.4 ng/ml in the 60-69 year old, and 6.3 ng/ml in the 70-79 year old men. Oesterling and colleagues also suggested a revision with age-specific reference values for serum PSA.[7] The recommended upper normal values were 2.5 ng/ml for men 40-49 years, 3.5 ng/ml for 50-59 years, 4.5 ng/ml for 60-69 years and 6.5 ng/ml for 70-79 years.

The influence of ethnicity on serum PSA has not been well-studied. Oesterling's study was limited to a population of white men.[7] The possible link between PSA and ethnicity is suggested by data demonstrating differences in incidence and death rates

Fig. 1.—Mean serum prostate-specific antigen concentration by 10-year age groups for Asian and white men.



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between Asian, black, Hispanic, and white populations.[1,8] As Asians represent the fastest growing minority group in the U.S., PSA normal value recommendations should be examined within the context of different ethnic groups in order to ascertain the effects of both age and ethnicity variables. This is especially important as the use of serum PSA values increasingly influence recommendations regarding referral and follow-up procedures for the diagnosis of prostate cancer. This pilot study was designed to assess the influence of age and ethnicity on serum PSA concentrations in Asian and white men living in the U.S. without a clinical diagnosis of prostate cancer.

Methods

Patients

Between October and December 1993, 1260 men who had serum PSA (Hybritech Tandem-R assay, San Diego, California) determinations at Straub Clinic & Hospital Department of Nuclear Medicine Radioimmunoassay Laboratory were initially identified as the cohort population. Patient name, age, and PSA concentration were obtained from the computer Laboratory Information System. The ethnicity of the patient was identified from the clinic and hospital computer demographic and schedule tracking system. The clinical diagnosis pertaining to disease of the prostate was obtained from review of each patient's clinic chart. Men who had a PSA value less than 10.0 ng/ml and who had no diagnosis of prostate cancer were selected for analysis. Ethnic categories included Asian and white men. Asian included Japanese, Korean, Filipino, and Chinese. Those who had mixed ancestry among these groups were included as Asian. Those who had mixed ancestry between any of these groups and other groups were not included in the study. Anyone with mixed ancestry between white and other groups was also not included. The final population sample consisted of 885 (70%) men aged 40 to 79 years.

Table 1.—Serum PSA Concentration and Patient Distribution by Age*

Age (years)	Patient No.	PSA (ng/ml)	
40 - 49	71	1.03†	(1.01, 1.06)‡
50 - 59	215	1.24	(1.23, 1.26)
60 - 69	323	2.17	(2.16, 2.18)
70 - 79	276	2.08	(1.68. 2.70)
Total	885	2.08	(1.95. 2.21)

*PSA indicates prostate-specific antigen
†Mean value
‡Numbers in parenthesis are the lower and upper values for the 95% confidence interval

Table 2.— Serum PSA Concentration by Age and Ethnicity*

	Asian		White	
Age Group	PSA (ng/ml)	95%C.I.	PSA (ng/ml)	95%C.I.
40 - 49	1.10†	(1.03, 1.17)‡	0.99†	(0.94, 1.03)‡
50 - 59	1.13	(1.11, 1.15)	1.36	(1.34, 1.38)
60 - 69	2.24	(2.22, 2.68)	2.09	(2.07, 2.11)
70 - 79	2.66	(2.65, 2.68)	2.73	(2.71, 2.75)
Total	210	(2.10, 2.11)	2.05	(2.05, 2.06)

*PSA indicates prostate-specific antigen
†Mean value
‡Numbers in parenthesis are the lower and upper values for the 95% confidence interval

Statistical analysis

Regression analysis was accomplished with the Statistical Analysis System (SAS) software, Regression Procedure, using the multiple regression and stepwise regression models with PSA as the predicted (dependent) variable and age and ethnicity as predictor (independent) variables. The PSA values were log (natural) transformed in order to better meet the linear assumptions of the regression model. The regression procedure calculated the Y intercept and the slope of the regression line. From this information it was possible to compute the predicted increase in PSA per year of age, both in absolute and relative terms. The software also calculated the multiple regression coefficient squared which indicates the proportion of the variance in PSA that is accounted for by age and ethnicity. The SAS Correlation Procedure computed the Pearson product moment coefficients of correlation (rho). This allowed paired comparisons of PSA and age and PSA and ethnicity. A p=0.05 was considered significant. The SAS software also calculated PSA means by different age and ethnicity groups and determined the cross-tabulations used in the analysis with 95% confidence intervals.

The mean + 2 SD was used as the upper limit of the estimated ranges for the serum PSA concentration for each 10-year age group.

Results

The PSA for the entire group of 885 men was 2.08 ± 2.0 ng/ml (mean +/- SD) (Table 1). The mean serum PSA concentration for each 10-year age group increased with age at the 95% level of confidence. Between 40-49 years, 2 (2.8%) had a serum PSA greater than 4.0 ng/ml; between 50-59 years, 5 (2.8%); between 60-69 years, 51 (15.8%); and between 70-79 years 69 (25.7%) had a serum PSA above 4.0 ng/ml. Overall, 127 men (14.7%) had a serum PSA greater than 4.0 ng/ml. PSA correlated with age (r=0.31; p=0.0001). Age accounted for 10% of the variance in serum PSA (p=0.0001). Using the regression formula, serum PSA increased 2.5% (0.06 ng/ml) per year of age.

The study group was about equally divided between white (49%) and Asian (51%) cases. Nearly three-fourths of the Asian men were of Japanese ethnicity. There was no direct correlation between serum PSA and ethnicity (r=0.03; p=0.3201). Ethnicity accounted for only 0.1% of the variance in PSA. Mean serum PSA for each age-specific group increased with age in both the Asian and white men (Fig 1). For age groups 40-49 and 60-69 years, mean PSA for the Asian cases was higher than white at the 95% level of confidence; for age groups 50-59 and 70-79 years, for white men were higher than Asian (Table 2). The age and ethnic-specific serum PSA ranges are shown in Table 3.

Discussion

Reference ranges for serum PSA in the published literature were derived from various populations of healthy men without clinically evident prostate cancer.[5-7] The validity of these parameters for the detection of early, and potentially curable prostate cancer have not been well-studied among the Asians. A possible link between PSA and ethnicity was suggested by a study conducted by Christmas, where the incidence of prostate cancer

Table 3.—Serum PSA Ranges by Age and Ethnicity*

	Total			Asian			White		
Age Group	PSA (ng/ml)	S.D.	Range	PSA (ng/ml)	S.D.	Range	PSA (ng/ml)	S.D.	Range
40 - 49	1.0†	0.7	0.0 - 2.4‡	1.1†	0.7	0.0 - 2.6‡	1.0†	0.6	0.0 - 2.2‡
50 - 59	1.2	1.0	0.0 - 3.3	1.1	0.8	0.0 - 2.7	1.4	1.3	0.0 - 3.9
60 - 69	2.2	2.0	0.0 - 6.1	2.2	2.0	0.0 - 6.2	2.1	1.9	0.0 - 5.9
70 - 79	2.7	2.3	0.0 - 7.2	2.7	2.2	0.0 - 7.0	2.7	2.4	0.0 - 7.4
All Ages	2.1	2.0	0.0 - 6.0	2.1	1.9	0.0 - 60	2.1	2.0	0.0 - 6.0

*PSA indicates prostate-specific antigen †Mean value ‡Range upper limit is mean + 2 S.D.

was shown to be particularly common among blacks in the U.S. and among Scandinavians, but rare among Japanese and other Asians.[8] More recent cancer statistics show that age-adjusted death rates for prostate cancer reported between 1988-1991 were highest in Switzerland, Sweden, and Norway and lowest in Japan, Hong Kong, and China.[1]

The increase in PSA with age demonstrated in this study has been observed by other investigators.[5-10] There was no consistent difference in serum PSA between Asian and white men without a clinical diagnosis of prostate cancer. PSA did not correlate with ethnicity (r=0.03, p=0.3210) and ethnicity was not predictive of PSA (0.1% of the variance). From a practical standpoint, the mean PSA levels were nearly identical overall for the Asian and white men. The age-specific range of PSA values for the two ethnic groups were very similar. Statistical differences between Asian and white PSA levels fluctuated for the age-specific groups and there was no consistent trend.

The retrospective, cross-sectional nature of our study is inappropriate for deriving reference ranges for PSA concentrations. Although patients with a diagnosis of prostate cancer were excluded from the study, the sample population cannot be considered healthy and prostate cancer-free. The fraction of patients with an abnormal PSA using the conventional cutoff value of 4.0 ng/ml and no clinical evidence of cancer by digital rectal examination (DRE), transrectal ultrasonography (TRUS), and prostate biopsy is unknown. In addition, patients with a normal DRE and PSA cannot be excluded from harboring prostate cancer. The significant expense of TRUS makes its use in the routine evaluation of patients with normal PSA and DRE impractical in the clinical practice at the study institution.

The investigators of this study attempted to decrease the level of uncertainty of undiagnosed prostate cancer cases by excluding patients with PSA greater than 10 ng/ml in our final analysis. The rationale for this rests on the observation that individuals with such values distort the true population of normal men at large.[9] In addition, men with values substantially greater than 10 ng/ml, and certainly values reaching the hundreds, have a higher likelihood of prostatic cancer. [6,10]

The study population was selected from an arbitrary fixed time frame. This permitted a sample of the large patient population at the clinic and hospital undergoing a PSA test. The inherent biases of the cross-sectional study applied across the Asian and white groups and still permitted a valid comparison of the two groups. The inclusion of men with a PSA greater than 4.0 ng/ml but with prostate cancer not yet diagnosed could inflate the calculated mean PSA values and ranges; the effect on the correlation and regression analysis values would be slight in the estimation of the authors.

Data on patient prostate size were not included in this study. Adjustment of the serum PSA for the size of the prostate gland may help to distinguish men with early prostate cancer from those with benign prostatic hypertrophy.[11] An ancillary study proposal to the National Cancer Institute Prostate, Lung, Colon, and Ovary cancer screening trial evaluating the the relationship between PSA, prostate size, and ethnicity in patients from Hawaii was recently approved for the investigators of this study.

Serum PSA is currently the most useful tumor marker for the diagnosis of prostate cancer, and is a potentially important screening test. Intensive efforts by researchers to identify cost-effective screening strategies incorporating the PSA test are ongoing. This preliminary study contributes to the understanding of PSA variation among individuals at risk for prostate malignancy with respect to ethnicity.

In summary, PSA increases with age in Asian and white men without a clinical diagnosis of prostate cancer but who are at risk for malignancy. No apparent difference was found in serum PSA between Asian and white men.

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